Also, there is provided a preferred tablet comprising an inner portion, preferably a core, which contains a cation of formula (I), and an outer portion which contains a salt of piperazine, completely surrounds the inner portion and is not uniform in thickness.

Thus, in the preferred tablet there is a depressi n in the outer portion, in the form of a hole or score, which does not extend to the inner portion; a depressi n may lie on one or both sides of the tablet.

Another preferred tablet is one wherein the thickness of the outer portion on one side of the tablet is substantially less than that on the other side.

In the preferred tablets the inner portion is found to be released more quickly and in particular the scored tablet is found to be convenient for administering a half dose by breaking the tablet along the score.

The tablet is found to be wholly effective in that the quaternary ammonium salt and the salt of piperazine each exert their respective ranges of activity, while the specific disadvantages of the quaternary ammonium salts are reduced. The tablet is especially useful for the treatment of worms in dogs.

The preferred tablet comprises an inner portion containing a salt of the *N,N*-dimethyl - *N* - 2 - phenoxyethyl - *N* - benzylammonium cation or the *N,N* - dimethyl-*N* - 2 - phenoxyethyl - *N* - 2^1 - thenylammonium cation, in particular, the *p* - chlorobenzenesulphonate salt of the *N,N* - dimethyl - *N* - 2 - phenoxyethyl - *N* - 2^1 - thenylammonium cation, and an outer portion containing the piperazine phosphate.

The effective unit dosage range of the tablet depends on a number of variable factors, for example the toxicity and effectiveness of the quaternary ammonium salt, of the cation of formula (I) and of the salt of piperazine, the nematode to be controlled, the mode and frequency of administration and the amount of inactive ingredients in the tablet. The inner and outer portions of the tablet each contain generally between 50 mg. and 2.5 g., and preferably between 50 mg. and 250 mg., of the cation of formula (I) in the quaternary ammonium salt and of piperazine base in the salt of piperazine.

According to the present invention in a further aspect, there is provided a method for the manufacture of the tablet comprising the application completely around the inner portion, which contains a quaternary ammonium salt containing a cation of formula (I), of the outer portion, which contains the salt of piperazine.

For example, the outer portion may be applied by compressing or moulding onto the inner portion the outer portion materials; or by spraying onto the inner portion and drying a solution or suspension of the outer portion materials in a volatile solvent, such as alcohol or acetone; or by spreading or sprinkling onto the inner portion, which is moistened by a liquid such as alcohol, acetone or alcoholic polyvinylpyrrolidine, the outer portion materials in a fine powder; or by dipping the inner portion into a liquid or paste preparation of the outer portion materials. Preferably the outer portion materials are compressed onto the inner portion.

According to the present invention in a further aspect, there is provided a method for the manufacture of the said preferred tablet comprising the compression onto the inner portion of the outer portion.

Thus, the preferred tablet may be manufactured by a method in which a compression coating machine is used. Outer portion materials, a pre-formed core containing the inner portion materials and more outer portion materials are fed successively into each die cavity in the machine, so that each die cavity contains the outer portion materials completely surrounding the core; the outer portion materials are then compressed. The depressed region in the outer portion is formed in any convenient manner: thus, suitable amounts of the outer portion materials are fed into each die cavity to form a tablet in which the thickness of the outer portion on one side is substantially less than on the other side; and a protrusion, preferably in the form of a point or ridge, is put on the face of each upper punch in the machine to form respectively a tablet with a hole or a score in the outer portion.

The core is preferably also formed by compression, so that the core and the preferred tablet may be formed successively using a compression coating machine. One unit of the machine forms the core and a second unit compresses the outer portion materials onto it, or one unit forms the core and is then adjusted so that the outer portion materials are compressed onto it.

The core materials and the outer portion materials may be formed by granulating respectively the quaternary ammonium salt containing the cation of formula (I) and the salt of piperazine, using a binding agent, for example, starch mucilage, potato starch,

sucrose, lactose or gelatin solution, and a lubricating agent, for example, magnesium stearate or talc.

The present invention will now be illustrated with reference to the accompanying drawings in which figures I, II, III and V are all vertical sections and figure IV is a plan view. It will be understood that the figures are only illustrative, are not necessarily to scale, and are not limiting on the scope of the present invention. In figure I is shown a tablet consisting of a core (1) which contains a quaternary ammonium salt containing a cation of formula (I) and an outer portion (2) which completely surrounds the inner portion and contains a salt of piperazine. In figure II is shown a preferred tablet consisting of an inner core (1) and an outer portion (2) whose thickness on one side of the tablet is substantially less than that on the other side. In figure III is shown a preferred tablet consisting of an inner core (1) and an outer portion (2) in which there is a hole (3) which does not extend to the inner core (1). In figure V is shown a preferred tablet consisting of an inner core (1) and an outer portion (2) in which there is a score (3) which does not extend to the inner core (1). In figure IV, which is a plan view of the tablet illustrated in figure V, is shown the score (3).

The invention will now be described with reference to the following examples, in which all temperatures are given in degrees Centigrade and the symbol # designates the standard size of the mesh of the sieve used, as defined in the British Pharmacopoeia, 1958, page 968.

EXAMPLE I

A tablet was made in the following manner:

a) *The Core*

N,N - Dimethyl - *N* - 2 - phenoxyethyl - *N* - 2[1] - thenylammonium *p* - chlorobenzenesulphonate	216.25 mg.
Alginic Acid	2.165 mg.
Potato Starch	43.25 mg.
Magnesium stearate	3.25 mg.

A mucilage of the acid in ten times its weight of water was made, and granulated with a fine powder of the *p*-chlorobenzenesulphonate, more water being added when necessary. The moist granules were successively sifted 20 # and dried at 55°. The dried granules were successively sifted 20 # and mixed with the starch and stearate.

b) *The Outer Portion*

Piperazine phosphate	260 mg.
Lactose	78 mg.
Dextrose monohydrate or sucrose	78 mg.
Potato starch	26 mg.
Magnesium stearate	5.2 mg.

A mixture of the phosphate, lactose and dextrose or sucrose was granulated with a mixture of water and industrial methylated spirits in equal parts. The moist granules were successively sifted 30 # and dried at 55°. The dried granules were sifted 30 # and mixed with the starch and stearate.

c) *The Tablet*

The core and the outer portion granules were compressed successively on a compression coating machine. A hole was formed in the outer portion by a pointed protrusion on the face of each punch in the machine.

The core of the tablet weighed 265 mg. and the outer portion 447 mg. The diameter of the tablet was 12.6 mm. and of the hole 4.0 to 6.0 mm. The depth of the tablet was 5.75 mm. and of the hole 1.5 to 2.0 mm.

EXAMPLE 2.

A tablet was made containing the following ingredients:

a) *The Core*

N - Benzyl - *N,N* - dimethyl - *N* - 2 - phenoxyethylammonium chloride	150 mg.
Potato starch	20 mg.
Magnesium stearate	1.5 mg.

Free flowing granules of the chloride were sifted 16#. The starch and stearate were added to and mixed with the granules.

b) *The Outer Portion*

Piperazine citrate	312.5 mg.
Sucrose	75 mg.
Magnesium Stearate	3.5 mg.

Fine powders of the citrate and sucrose were mixed and granulated with an aqueous alcoholic gelatin solution. The granules were sifted 20#, the moist granules dried at 55°, and the dried granules sifted 20#. The stearate was added to and mixed with the dried granules.

The core and outer portion granules were compressed successively on a compression-coating machine, to form a tablet with a core weight of 170 mg. and an outer portion weight of 400 mg.

EXAMPLE 3.

A tablet was made in the following manner:

a) *The Core*

The core was made of the same materials and contained the same quantity of materials as Example I a.

b) *The Outer Portion*

The outer portion was made of the same materials and contained the same quantity of materials as Example I b.

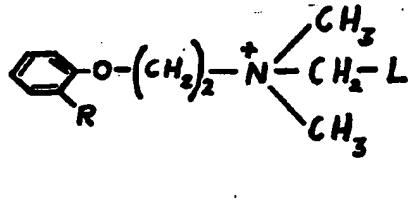
c) *The Tablet*

The core and the outer portion granules were compressed successively on a compression coating machine. A score was made in the outer portion by a ridge, suspending an angle of 55° at its apex, on the face of each punch in the machine.

The core of the tablet weighed 265 mg. and the outer portion 447 mg. The diameter of the tablet was 12.6 mm. and that of the score 10.2 mm. The score was 11.1 mm. in length, its greatest width 1.4 mm. and had a depth of 1 mm.

WHAT WE CLAIM IS:—

1. A method for the manufacture of a tablet comprising the application of an outer portion, which contains a therapeutically acceptable salt of piperazine, completely around an inner portion, which contains a therapeutically acceptable quaternary ammonium salt having a cation of formula (I),



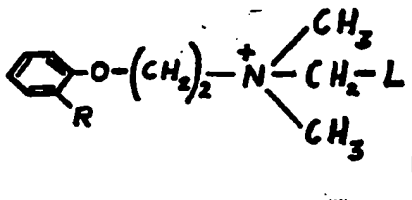
(I)

wherein R is a hydrogen, chlorine or bromine atom or a methyl or nitro group when L is a phenyl group optionally substituted in the *ortho* position with a chlorine, bromine or fluorine atom, or a methyl group, or R is a hydrogen or halogen atom or a methyl or nitro group when L is a thienyl group.

2. A method for the manufacture of a tablet as claimed in claim 1 comprising the compression of the outer portion onto the inner portion.

3. A method for the manufacture of a tablet as claimed in claim 2 wherein the inner portion is in the form of a core.

4. A tablet comprising an inner portion which contains a therapeutically acceptable quaternary ammonium salt having a cation of formula (I)



(I)

wherein R is a hydrogen, chlorine, or bromine atom or a methyl or nitro group when L is a phenyl group optionally substituted in the *ortho* position with a chlorine, bromine or fluorine atom r a methyl group, or R is a hydrogen or halogen atom or a methyl or nitro group when L is a thienyl group, and an uter portion which completely surrounds the inner portion and contains a therapeutically acceptable salt of piperazine.

5. A tablet as claimed in claim 4 wherein the outer portion is not uniform in thickness.

6. A tablet as claimed in claim 5 wherein the thickness of the outer portion on one side of the tablet is substantially less than that on the other side.

7. A tablet as claimed in claim 5 which has a depression in the outer portion.

8. A tablet as claimed in claim 7 wherein the depression is a hole.

9. A tablet as claimed in claim 7 wherein the depression is a score.

10. A tablet as claimed in any one of claims 4 to 9 wherein the inner portion contains a salt of the *N,N* - dimethyl - *N* - 2 - phenoxyethyl - *N* - benzylammonium cation.

11. A tablet as claimed in any one of claims 4 to 9 wherein the inner portion contains a salt of the *N,N* - dimethyl - *N* - 2 - phenoxyethyl - *N* - 2^1 - thenylammonium cation.

12. A tablet as claimed in claim 11 wherein the inner portion contains the *p*-chlorobenzenesulphonate salt of the *N,N* - dimethyl - *N* - 2 - phenoxyethyl - *N* - 2^1-thenylammonium cation.

13. A tablet as claimed in any one of claim 4 to 12 wherein the outer portion contains piperazine phosphate.

14. A tablet substantially as hereinbefore described with reference to the examples and accompanying drawings.

15. A method for the manufacture of a tablet according to claim 4 substantially as hereinbefore described or ascertained.

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(Agent for the Applicants)
(Chartered Patent Agent)

Reference has been directed in pursuance of Section 9, subsection (1) of the Patents Act, 1949, to patent No. 829,507.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press (Leamington) Ltd.—1965. Published by The Patent Office, 25 Southampton Buildings, London, W.C.2, from which copies may be obtained.

994742 COMPLETE SPECIFICATION

1 SHEET *This drawing is a reproduction of the Original on a reduced scale*

Fig. I

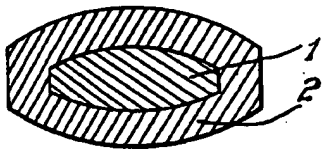

Fig. II

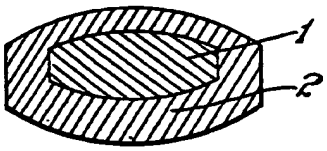

Fig. III

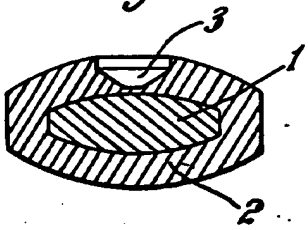

Fig. IV

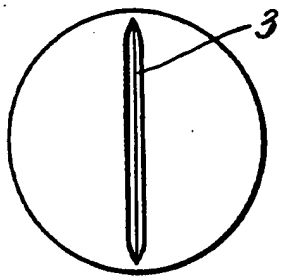

Fig. V